

REMARKS

Claims 1-13 were pending in this application. Claims 6-13 have been canceled without prejudice. Claims 1, 2, and 4 have been amended, claims 2 and 5 have also been canceled, and new claims 14-23 have been added. Accordingly, upon entry of this amendment, claims 1, 2, 4, and 14-23 will be pending.

Any amendments to and/or cancellation of the claims are not to be construed as acquiescence to any of the rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

Support for the amendments to the claims may be found throughout the specification and claims, as originally filed. Specifically, support for the amendment to claims 1 to recite “an XBP-1 deficient mouse” can be found, for example, in originally filed claim 3; support for the amendment to claim 1 to recite “stimulate” may be found, for example, in originally filed claim 5; support for new claims 7-13 may be found, for example, at page 27, last paragraph, through page 28, first paragraph; support for new claim 14, can be found, for example, at page 8, first paragraph; and support for new claims 22 and 23 may be found at, for example, page 54, last full paragraph, through page 56, first full paragraph of the specification. *No new matter has been added.*

Election/Restriction

Group II (claims 1, 4, and 5) was elected by Applicants with traverse. Applicants gratefully acknowledge the Examiner’s indication that Group I (claims 1-3, and 5) will be rejoined with Group II.

Applicants also acknowledge the Examiner’s indication that claims 6-13 have been withdrawn from further consideration as being directed to a non-elected invention, there being no allowable or linking generic claim. Accordingly, claims 6-13 have been canceled herein.

Priority

The Examiner has requested that the status of the parent application of the instant application be updated in the specification. Applicants have amended the specification to indicate that the parent, application, U.S. 09/753,346, is now U.S. Patent No. 6,632,608. Accordingly, Applicants respectfully request this objection to the specification be withdrawn.

Information Disclosure Statement

The Examiner is of the opinion that “[t]he information disclosure statement filed 6/14/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed.”

Applicants respectfully submit that the Information Disclosure Statement (IDS) filed June 14, 2006 complies with the requirements of 37 CFR § 1.98(a)(2). As stated in MPEP § 609,

a copy of any patent, publication, or other information listed in an information disclosure statement is not required to be provided if it was previously cited by or submitted to the Office in a prior application, provided that the prior application is properly identified in the statement and relied on for an earlier filing date under 35 U.S.C. 120.

All of the references listed in the Form PTO SB-08 submitted to the Office June 14, 2006 were previously submitted to the Examiner during the prosecution of the parent application (09/753,346). The instant application was also properly identified in the IDS accompanying that Form PTO SB-08. Although one additional reference was added to the SB-08 (C61) submitted June 14, 2006, that reference was provided, and indicated as such on that IDS. Nevertheless, for the Examiner’s convenience, Applicants submit herewith, copies of all foreign patent documents and non-patent literature cited in the SB-08 (B1-B2, C1-C61)

The Examiner is further of the opinion that “C16 through C20 of the information disclosure statement filed 6/14/2006 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the publication date for these references is missing.”

Applicants respectfully submit that the GenBank search reports cited as references C16-C20 were provided to assist the Examiner in understanding the relevance of the GenBank records cited in the Form PTO SB-08. Applicants respectfully submit that the above information should be adequate to assist the Examiner in considering these references. However, for the Examiner's convenience, Applicants submit herewith a substitute PTO SB-08 form in which references C16-C20 have been cited in the format consistent with 37 C.F.R. §1.98.

In view of all of the above, Applicants respectfully request that the Examiner review the cited references and initial and return to Applicants the attached PTO SB-08 form signifying that the aforementioned references have been considered and made of record.

Rejection of Claims 1-5 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-5 under 35 U.S.C. §112, first paragraph because, according to the Examiner, "[t]he claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." In particular, the Examiner is of the opinion that

the claimed invention does not appear to be enabled for the intended use,
i.e. finding compounds that remedy the XBP-1 deficiency.

Applicants respectfully traverse this rejection for at least the reasons set forth below. Claim 1 as amended, and claims dependent therefrom, are directed to methods of identifying a compound that *stimulates* hepatocyte growth or plasma cell differentiation or Th2 cell subset activity comprising contacting hepatocytes or B cells or T cells from *an XBP-1 deficient mouse*, with a test compound; and determining the effect of the test compound on the growth of the hepatocytes or differentiation of the B cells into plasma cells or Th2 cytokine production by the T cells, the test compound being identified as a modulator of hepatocyte growth or plasma cell differentiation or Th2 cell subset activity based on the ability of the test compound to *stimulate* the growth of the hepatocytes or differentiation of the B cells or Th2 cytokine production by the T cells from *the XBP-1 deficient mouse*. Applicants submit that, based on the teachings in Applicants' specification and the knowledge generally available in the art at the time of the invention, one of ordinary skill

in the art would be able to perform the claimed screening assays using no more than routine experimentation.

With respect to the scope of the invention, the Examiner is of the opinion that the term

“modulation” encompasses both suppression and stimulation. However, according to the teaching of the specification the XBP-1 deficient hepatocytes are poorly developed, and dying, it is hard to imagine that their growth could be further down-regulated.

In contrast to the Examiner’s assertion, Applicants respectfully submit that the scope of the claims is commensurate with the disclosure in Applicants’ specification. However, without acquiescing to the validity of the Examiner’s rejection and solely in the interest of expediting prosecution, Applicants have amended claim 1, and claims dependent therefrom, to recite the term “stimulate” rendering this portion of the Examiner’s rejection under 35 U.S.C. §112, first paragraph moot.

With respect to the amount of guidance provided in Applicants’ specification, the Examiner is of the opinion that

the only XBP-1 deficient hepatocytes taught in the specification were obtained from the embryos of the XBP-1 gene knockout mice (XBP-1^{-/-}) because XBP-1 gene knockout is lethal and the embryo would not survive to mature; and the only XBP-1 deficient lymphocytes (T/B cells) were obtained from XBP-1^{-/-}/RAG-2 chimeric mice, made by injecting mouse XBP-1^{-/-} ES cells to RAG-2 blastocyst, and through a mechanism called RAG-2-deficient blastocyst complementation. ***The specification does not provide sufficient guidance for any other means of obtaining XBP-1 deficient cells.*** (Emphasis added).

Applicants respectfully submit that the teachings in the specification provide sufficient guidance to allow one of ordinary skill in the art to generate XBP-1 deficient mice and isolate cell from such animals for use in the claimed methods.

More specifically, Applicants’ specification teaches that a non-human XBP-1-deficient mouse can be produced by homologous recombination or blastocyst complementation, techniques conventionally known in the art at the time of filing. In particular, at page 23, first full paragraph, through page 24, Applicants’ specification teaches that

[n]on-human animals deficient in a particular gene product typically are created by homologous recombination. Briefly, a vector is prepared which contains at least a portion of the XBP-1 gene into which a deletion, addition or substitution has been introduced to thereby alter, e.g., functionally disrupt, the endogenous XBP-1 gene. The XBP-1 gene preferably is a mouse XBP-1 gene. For example, a mouse XBP-1 gene can be isolated from a mouse genomic DNA library using the mouse XBP-1 cDNA as a probe. The mouse XBP-1 gene then can be used to construct a homologous recombination vector suitable for altering an endogenous XBP-1 gene in the mouse genome. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous XBP-1 gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous XBP-1 gene is mutated or otherwise altered but still encodes functional protein (e.g., the upstream regulatory region can be altered to thereby alter the expression of the endogenous XBP-1 protein). In the homologous recombination vector, the altered portion of the XBP-1 gene is flanked at its 5' and 3' ends by additional nucleic acid of the XBP-1 gene to allow for homologous recombination to occur between the exogenous XBP-1 gene carried by the vector and an endogenous XBP-1 gene in an embryonic stem cell. The additional flanking XBP-1 nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see e.g., Thomas, K.R. and Capecchi, M. R. (1987) *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced XBP-1 gene has homologously recombined with the endogenous XBP-1 gene are selected (see e.g., Li, E. et al (1992) *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (see e.g., Bradley, A. in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E.J. Robertson, ed. (ERL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, A. (1991) *Current Opinion in Biotechnology* 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec et al.; WO 91/01140 by Smithies et al; WO 92/0968 by Zijlstra et al.; and WO 93/04169 by Berns et al.

Applicants' specification further teaches at page 22, first paragraph,

a "conditional knock-out" system, in which the XBP-1 gene is rendered non-functional in a conditional manner, can be used to create XBP-1 deficient hepatocytes (or hepatocyte precursors) for use in screening assays. For example, a tetracycline-regulated system for conditional disruption of a gene as described in WO 94/29442 and U.S. Patent No. 5,650,298 can be used to create hepatocytes (or hepatocyte precursors), or XBP-1 deficient animals from which hepatocytes (or hepatocyte precursors) can be isolated, that can be rendered XBP-1 deficient in a controlled manner through modulation of the tetracycline concentration in contact with the cells. For assays relating to plasma cell differentiation or T cell subset activity, a similar conditional disruption approach can be used or, alternatively, the RAG-2 deficient blastocyst complementation system can be used to generate mice with lymphoid organs that arise from embryonic stem cells with homozygous mutations of the XBP-1 gene (see Example 2). XBP-1 deficient lymphoid cells (e.g., thymic, splenic and/or lymph node cells) or purified XBP-1 deficient B cells or T cells from such animals can be used in screening assays.

Moreover, as acknowledged by the Examiner, Applicants have provided working Examples teaching the production of mice deficient in XBP-1. Specifically, Example 1 teaches the generation of XBP-1 knock-out mice by disruption of the endogenous XBP-1 gene in embryonic stem cells (see page 56, last paragraph, through page 57, first paragraph). Example 2, teaches the generation of a conditional knock-out allele of the XBP-1 gene and the production of chimeric mice using Rag-2 deficient blastocysts.

Thus, Applicants submit that the phrase XBP-1 deficient mice encompasses a well-defined number of deficient mice with XBP-1 knock-out mice, XBP-1 conditional knock-out mice, and XBP-1 chimeric mice being representative.

Moreover, the Examiner has not proven that the methods of the invention, as described in the instant specification for the species of XBP-1 knock-out mice, XBP-1 conditional knock-out mice, and XBP-1 chimeric mice, would not work the same way as for other XBP-1 deficient mice. See M.P.E.P. § 2164.02 which states that

[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the

examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation. (Emphasis added).

In view of all of the foregoing, it is evident that Applicants' specification contains sufficient teachings to enable one of skill in the art to make and use the claimed method.

Applicants would also like to make the following of record with respect to the Examiner's assertions regarding the production of XBP-1 deficient animals in a mammalian species other than a mouse. Applicants respectfully submit that, at the time the invention was made, the teachings of the specification with regard to how to make XBP-1 deficient non-human mammals (see, *e.g.*, page 23, first full paragraph), had been *successfully* used by many groups in the production of a variety of mammals, including rats, pigs, sheep, and cows. Applicants refer the Examiner to:

Hammer *et al.* (*J. Anim. Sci.* 63(1): 269-278, 1986; attached herewith as Appendix A), which teach the production by microinjection of transgenic rabbits, sheep and pigs expressing human growth hormone under the control of the mouse metallothionein-I promoter;

Pursel *et al.* (*J. Reprod. Fertil. Suppl.* 41: 77-87, 1990; attached as Appendix B), which teach the production by microinjection of transgenic pigs expressing bovine and human growth hormone under the control of the mouse metallothionein-I promoter;

Rexroad *et al.* (*J. Anim. Sci.* 69: 2995, 1991; attached herewith as Appendix C), which teach the production, by microinjection, of transgenic sheep expressing bovine growth hormone or human growth hormone-releasing factor under the control of the mouse transferrin promoter or the mouse albumin promoter, respectively; and

Ebert *et al.* (*Bio/Technology* 9: 835, 1991; attached herewith as Appendix D), which teach the production, by microinjection, of transgenic goats expressing longer acting tissue plasminogen activator under the control of the murine whey acid promoter.

Each of these references demonstrates the efficacy of the methodologies of homologous recombination as taught in the instant specification in the production of non-human mammals. Thus, it is clear from the teachings of these references that the methodologies taught by Applicants enable the production of animals other than mice which are deficient in XBP-1.

Nonetheless, in the interest of expediting prosecution of the application and in no way acquiescing to the validity of the Examiner's rejection, claim 1, and claims dependent therefrom, have been amended such that they are now directed to "XBP-1 deficient mice" and, thus, the Examiner's rejection to the specification as not being enabled because "only XBP-1 deficient mice were readily available" has been rendered moot.

The Examiner is further of the opinion that

although not explicitly indicated, the use of the XBP-1 deficient cells implies or mandates any compound that regulates the function of these cells must be capable of supplementing the function of XBP-1 because any dysfunction in these cells are caused by the missing XBP-1 gene, and thus "modulating" the function of these cells requires providing the function of XBP-1 gene. To this end, it is noted other than the XBP-1 gene itself, the specification fails to teach and one cannot envision what other compounds may substitute or supplement the XBP-1 gene. For example, such compound is apparently not present in the body of a mouse since the XBP-1 deficiency bring to a halt the embryo development of the mouse, and lethal. ***The specification fails to provide sufficient guidance as to what type of compound(s) one should look for as a possible candidate to modulate XBP-1 deficiency***, and the skilled intending to practice the invention will be sent to an extensive hunting journey. (Emphasis added).

Applicants respectfully submit that this portion of the Examiner's rejection appears to be focused on a perceived lack of description of specific compounds in the present specification when, in fact, *the claimed invention is directed to screening methods* and not the compounds that are identified by these screening methods. In particular, as amended claim 1, and claims dependent therefrom, are directed to ***methods of identifying a compound*** that stimulates hepatocyte growth or plasma cell differentiation or Th2 cell subset activity comprising contacting hepatocytes or B cells or T cells from an XBP-1 deficient mouse, with a test compound, and determining the effect of the test compound on the growth of the hepatocytes or differentiation of the B cells into plasma cells or Th2 cytokine production by the T cells, the test compound being identified as a modulator of hepatocyte growth or plasma cell differentiation or Th2 cell subset activity based on the ability of the test compound to stimulate the growth of the hepatocytes or differentiation of the B cells or Th2 cytokine production by the T cells from the XBP-1 deficient mouse.

In contrast to the Examiner's assertions, Applicants respectfully submit that the scope of the claims is commensurate with the disclosure in Applicants' specification and Applicants have provided an amount of guidance sufficient to enable one of skill in the art to practice the *claimed screening methods* of the invention without undue experimentation. Specifically, Applicants' specification provides ample guidance to one of skill in the art on *screening assays*, *test compounds* suitable for the use in such assays, and provides *exemplary assays* to determine whether a test compound modulates hepatocyte growth or plasma cell differentiation or Th2 cell subset activity.

The instant invention is based, at least in part, on the discovery that mice lacking XBP-1 have severely impaired hepatocyte development, are severely impaired in plasma cell generation and exhibit defects in production of Th2 cytokines. Based on Applicants' identification of XBP-1 as a transcription factor essential for hepatocyte growth, plasma cell differentiation and Th2 cell subset activity and given the teachings of Applicants' specification, one of ordinary skill in the art would have understood that Applicants were in possession of the claimed screening assays, *i.e.*, that compounds identified using the claimed assays will modulate hepatocyte growth, plasma cell differentiation and/or Th2 cell subset activity by means other than modulating XBP-1 itself, *i.e.*, rescuing the XBP-1 deficient phenotype.

Applicants' specification teaches a variety of such screening assays and methods to produce the animals and cell derived therefrom for use in such assays (as described above). For example, page 21, last paragraph, through page 28, first paragraph of the specification teaches methods to generate XBP-deficient animals, and assays using cell deficient in XBP-1.

Furthermore, Applicants' provide working examples of assays to determine whether a test compound modulates hepatocyte growth, plasma cell differentiation and regulation of T cell subsets. For example, Example 1, at page 59 of the specification teaches assays to determine whether a compound stimulates hepatocyte growth, Example 2, at pages 64 and 65 of the specification, teach assays to determine whether a compound stimulates plasma cell differentiation, and Example 4, at page 68 of the specification, teach assays to determine whether a compound modulates Th2 cell subset activity. Accordingly, Applicants have described a genus of screening assays within the scope of the pending claims.

Applicants also provide examples of compounds that can be tested in the claimed

methods. For example beginning at page 29, second full paragraph, Applicants' specification teaches that test compounds suitable for use in the screening methods of the invention include "peptides, nucleic acids, carbohydrates, small organic molecules, and natural product extract libraries." Moreover, Applicants refer the Examiner to page 28, first full paragraph, through page 29, first full paragraph of the specification where Applicants identify extant, art-recognized libraries of such compounds, exemplify the production of libraries of such compounds, and describe well known methods for generating such libraries of test compounds.

Applicants also point out that the nature of a screening assay is such that a variety of different compounds are tested for their ability to affect a parameter of interest and are selected as giving a positive or negative result on that basis. Screening assays are designed to identify compounds that have a desired effect or activity and, thus, do not require that one have an *a priori* knowledge of which compounds will be selected as positive or negative. The fact that some compounds will modulate hepatocyte growth, plasma cell differentiation, and/or Th2 cell subset activity (and be selected, *i.e.*, for further evaluation) and some compounds will not modulate T- hepatocyte growth, plasma cell differentiation, and/or Th2 cell subset activity (and, thus, will not be selected, *i.e.*, for further evaluation) is precisely the reason for performing the assay.

Furthermore, the U. S. Patent Office has recognized that screening assay claims having no limitation as to the compounds to be tested are patentable (see, for example, United States Patents 6,090,544 and 6,117,645, attached as Appendices E and F, respectively). Accordingly, the fact that the compounds to be identified in the claimed screening assays are not specifically described in the application does not in any way imply that the claimed screening assays are inadequately described.

Accordingly, Applicants provide sufficient guidance such that one of ordinary skill in the art could practice the methods claimed without undue experimentation.

In summary, Applicants respectfully submit that based on the teachings and guidance provided by Applicants in the specification in combination with the general knowledge available to one of skill in the art at the time the application was filed, one of skill in the art would be able to make and use an *XBP-1 deficient mouse* and perform the *claimed screening assays* using no more than routine experimentation. As stated in *Forman*, "[t]he test is not merely quantitative, since a

considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *Ex parte Forman*, 230 USPQ 546, 547 (Bd. App. 1986). As also pointed out by the Federal Circuit in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (1990), "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." 15 USPQ 2d at 1329. See, also *In re Brana*, 34 USPQ 2d 1436 (Fed. Cir. 1995).

In view of the ample guidance provided in the specification and the references cited therein, and the extensive knowledge available in the art for the generation of *mice deficient in XBP-1*, the instant specification enables a person of ordinary skill in the art to make and use the *claimed screening methods* without undue experimentation. Accordingly, Applicants respectfully submit that pending claims fulfill the 35 U.S.C. §112, first paragraph requirements and, therefore, respectfully request reconsideration and withdrawal of the foregoing rejection of claims 1-5.

Double Patenting

The Examiner has provisionally rejected claims 1-5 under the judicially created doctrine of obviousness-type double patenting as being "unpatentable over claim 28 of U.S. Application No. 10/655,620." The Examiner states that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because they overlap in scopes."


Applicants respectfully submit that upon an indication of allowable subject matter in this or U.S. Application No. 10/655,620, Applicants will consider filing a terminal disclaimer, if appropriate.

SUMMARY

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' Attorney at (617) 227-7400.

Dated: January 26, 2007

Respectfully submitted,

By 
Elizabeth A. Hanley, Reg. No. 33,505
for Megan E. Williams, Reg. No. 43,270
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicants